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L2      344687 L1 AND (VASCULAR DISEASE) OR STROKE OR VASOSPASM OR
(HEAD INJURY
               )

=> S (VASCULAR DISEASE) OR STROKE OR VASOSPASM OR (HEAD INJURY)
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L5   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2005:563127  CAPLUS
DN   143:108822
TI   Cytochrome P-450: a new target in the heart and coronary
circulation
AU   Doggrell, S. A.
CS   School of Biomedical Sciences, University of Queensland, QLD,
4072,
     Australia
SO   Drugs of the Future (2005), 30(3), 261-269
     CODEN: DRFUD4; ISSN: 0377-8282
PB   Prous Science
DT   Journal; General Review
LA   English
AB   A review.  Cytochrome P 450 enzymes (CYPs) are present in the
heart and
     coronary circulation.  The activation of CYP2J2/3 to increase
the production
     of epoxyeicosatrienoic acids (EETs) may be cardioprotective in
cardiac
     ischemia and reperfusion.  On the other hand, inhibition of
CYP2C9 with
     cimetidine, or more selectively with sulfaphenazole, is
cardioprotective
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in the perfused rat heart. In a dog model of cardiac ischemia and reperfusion, inhibitors of CYP o-hydroxylases (e.g., CYP4A, CYP4F) reduce infarct size. Inhibition of selected CYPs as an approach to the treatment of myocardial infarction should therefore be further developed. The function of CYPs in the coronary artery and other blood vessels is varied and complex, and only just beginning to be elucidated. In the coronary artery, when nitric oxide (NO) bioavailability is inhibited, the activity of CYPs may be increased, with the production of vasodilatory EETs. Conversely, when CYP2C9 is inactivated in humans with coronary artery disease (CAD), acetylcholine-induced NO-mediated vasodilatation is enhanced. In the presence of CAD/oxidized LDL, the EET vasodilatory system may be inhibited. Drugs that target CYPs and/or EETs are thus expected to be useful in the elucidation of the role of this system, and may also have therapeutic utility.

RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 1
AN 2004095780 MEDLINE
DN PubMed ID: 14634044
TI Catalytic activity and isoform-specific **inhibition** of rat cytochrome **p450 4F** enzymes.
AU Xu Fengyun; Falck John R; Ortiz de Montellano Paul R; Kroetz Deanna L
CS Department of Biopharmaceutical Sciences, University of California, San Francisco, CA 94143-0446, USA.
NC GM-25515 (NIGMS)
GM-31278 (NIGMS)
HL-53994 (NHLBI)
P30 DK26743 (NIDDK)
SO The Journal of pharmacology and experimental therapeutics, (2004 Mar) Vol. 308, No. 3, pp. 887-95. Electronic Publication: 2003-11-21.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 200404
ED Entered STN: 20040302
Last Updated on STN: 20040407
Entered Medline: 20040406
AB Arachidonic acid is omega-hydroxylated to 20-hydroxyeicosatetraenoic acid (20-HETE), which has effects on vasoactivity and renal tubular transport and has been implicated in the regulation of blood pressure. Cytochrome p450 (p450) 4A isoforms are generally considered the major arachidonic acid omega-hydroxylases; however, little is known about the role of rat CYP4F isoforms in 20-HETE formation. The rat CYP4F isoforms, CYP4F1, CYP4F4, CYP4F5, and CYP4F6, were heterologously expressed in Escherichia coli, and their substrate specificity in fatty acid metabolism was characterized. Substrate-binding assays indicated that leukotriene B(4) (LTB(4)) and arachidonic acid bound CYP4F1 and CYP4F4 in a type-I manner with a K(s) of 25 to 59 microM, and lauric acid bound CYP4F4 poorly. Reconstituted CYP4F1 and CYP4F4 catalyzed the omega-hydroxylation of LTB(4) with a K(m) of 24 and 31 microM, respectively, and CYP4F5 had minor activity in LTB(4) metabolism. Importantly, CYP4F1 and CYP4F4 catalyzed the omega-hydroxylation of arachidonic acid with an apparent k(cat) of 9 and 11 min(-1), respectively. Lauric acid was a poor substrate for all of the CYP4F isoforms, and CYP4F6 had no detectable fatty acid omega-hydroxylase activity. The p450 omega-hydroxylase inhibitors 17-octadecynoic acid, 10-undecynyl sulfate, and N-methylsulfonyl-12,12-dibromododec-11-enamide showed isoform-specific inhibition of CYP4F1- and CYP4F4-catalyzed omega-hydroxylation of arachidonic acid and potency differences between the CYP4A and CYP4F isoforms. These data support a significant role for CYP4F1 and CYP4F4 in the formation of 20-HETE and identify p450 inhibitors that can be used to understand the relative contribution of the CYP4A and CYP4F isoforms to renal 20-HETE formation.

L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:822150 CAPLUS
DN 141:378078
TI Inhibition of Cytochrome P450ω-Hydroxylase A novel endogenous cardioprotective pathway
AU Nithipatikom, Kasem; Gross, Eric R.; Endsley, Michael P.; Moore, Jeannine M.; Isbell, Marilyn A.; Falck, John R.; Campbell, William B.; Gross, Garrett J.
CS Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, USA
SO Circulation Research (2004), 95(8), e65-e71
CODEN: CIRUAL; ISSN: 0009-7330
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Cytochrome P450s (CYP) and their arachidonic acid (AA) metabolites have important roles in regulating vascular tone, but their function and specific pathways involved in modulating myocardial ischemia-reperfusion injury have not been clearly established. Thus, the authors characterized the effects of several selective CYPω-hydroxylase inhibitors and a CYPω-hydroxylase metabolite of AA, 20-hydroxyeicosatetraenoic acid (20-HETE), on the extent of ischemia-reperfusion injury in canine hearts. During 60 min of ischemia and particularly after 3 h of reperfusion, 20-HETE was produced at high concns. A nonspecific CYP inhibitor, miconazole, and 2 specific CYPω-hydroxylase inhibitors, 17-octadecanoic acid (17-ODYA) and N-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS), markedly inhibited 20-HETE production during ischemia-reperfusion and produced a profound reduction in myocardial infarct size (expressed as a percent of the area at risk) (19.6±1.7% [control], 8.4±2.5% [0.96 mg/kg miconazole], 5.9±2.2% [0.28 mg/kg 17-ODYA], and 10.8±1.8% [0.40 mg/kg DDMS], P<0.05, resp.). Conversely, exogenous 20-HETE administration significantly increased infarct size (26.9±1.9%, P<0.05). Several CYPω-hydroxylase isoforms, which are known to

produce 20-HETE such as CYP4A1, CYP4A2, and CYP4F, were demonstrated to be present in canine heart tissue and their activity was markedly inhibited by incubation with 17-ODYA. These results indicate an important endogenous role for CYPω-hydroxylases and in particular their product, 20-HETE, in exacerbating myocardial injury in canine myocardium.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L5 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2004:288125 BIOSIS
DN PREV200400286882
TI Norepinephrine-induced phospholipase D activation is independent of cytochrome P450 4A and 4F in aortic vascular smooth muscle cells.
AU Parmentier, Jean-Hugues [Reprint Author]; Malik, Kafait U
CS Pharmacology, University of Tennessee, 874 Union Avenue, Memphis, TN, 38163, USA
jparmentier@utmem.edu
SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 171.16. http://www.fasebj.org/. e-file.
Meeting Info.: FASEB Meeting on Experimental Biology: Translating the Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.
ISSN: 0892-6638 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jun 2004
Last Updated on STN: 16 Jun 2004
AB Norepinephrine (NE) stimulates phospholipase D (PLD) activity via phospholipase A2-dependent arachidonic acid (AA) release in rabbit aortic vascular smooth muscle cells (VSMC). Exogenous 20-hydroxyeicosatetraenoic acid, an eicosanoid generated through the cytochrome P450 (CYP) 4A pathway, stimulates PLD activity. This study was conducted to determine if endogenous CYP4-derived AA metabolites act as intracellular mediators of NE-induced PLD activation in VSMC. Rabbit VSMC CYP4A and CYP4F isoforms were depleted with antisense oligonucleotides (ODN) treatment for 48 hours. CYP4A or **CYP4F** depletion did not **inhibit**

NE-induced PLD activation but rather enhanced to a similar degree (20%)
basal as well as NE-induced PLD activity. The corresponding CYP4A and
CYP4F sense ODN did not alter CYP levels and basal or NE-induced PLD
activity. CYP4A inducers, fenofibrate (100 muM) and Wy 14643 (10 muM),
inhibited (20%) the basal and NE-induced PLD activity. These data suggest
that PLD activation is independent of the CYP4A/4F pathway and that a
CYP4-derived AA metabolite(s) maintains an inhibitory effect on basal PLD
activity in rabbit VSMC. (USPHS Grant-19134, NIH-HLBI and AHA-Southeast
Affiliate).

L5 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:765629 CAPLUS
DN 141:293982
TI Cytochrome P450 4Fs: response and role following brain trauma
AU Strobel, H. W.; Kalsotra, A.; Dash, P. K.
CS Department of Biochemistry and Molecular Biology, The University of
Texas-Houston Medical School, Houston, TX, USA
SO Cytochromes P450: Biochemistry, Biophysics and Drug Metabolism, International Conference on Cytochromes P450, 13th, Prague, Czech Republic, June 29-July 3, 2003 (2003), Meeting Date 2003, 107-114.
Editor(s): Anzenbacher, Pavel; Hudecek, Jiri. Publisher: Monduzzi Editore,
Bologna, Italy.
CODEN: 69FTSZ; ISBN: 88-323-3142-X
DT Conference; (computer optical disk)
LA English
AB Following TBI, the expression of CYP4F proteins in lung, liver and kidney
show tissue specific effects. CYP4F expression and associated LTB4 ω
hydroxylase activity increase markedly in the lung, less markedly but
significantly in the kidney while no change is observed in the liver. LTB4
degradation by CYP4F enzymes seems to be a central pathway involved in
modulating inflammatory response after brain trauma.
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L5 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 2
AN 2001256258 MEDLINE

DN PubMed ID: 11353747
TI A novel cytochrome P450 enzyme responsible for the metabolism of ebastine
in monkey small intestine.
AU Hashizume T; Mise M; Matsumoto S; Terauchi Y; Fujii T; Imaoka S; Funae Y;
Kamataki T; Miyazaki H
CS Developmental Research Laboratories, Dainippon Pharmaceutical Co., Ltd.,
Osaka, Japan.. takanori-hashidume@dainippon-pharm.co.jp
SO Drug metabolism and disposition: the biological fate of chemicals, (2001
Jun) Vol. 29, No. 6, pp. 798-805.
Journal code: 9421550. ISSN: 0090-9556.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010903
Last Updated on STN: 20010903
Entered Medline: 20010830
AB Small intestinal microsomes of cynomolgus monkeys were found to catalyze
hydroxylation and dealkylation of an H(1)-antihistamine prodrug, ebastine.
To identify the main enzyme responsible for ebastine hydroxylation, which
has been hitherto unknown, we purified two cytochrome P450 isoforms, named
P450 MI-2 and P450 MI-3, from the intestinal microsomes on the basis of
the hydroxylation activity. P450 MI-2 and P450 MI-3 showed the respective
apparent molecular weights of 56,000 and 53,000 on sodium dodecyl
sulfate-polyacrylamide gel electrophoresis. The internal amino acid
sequence of P450 MI-2 had high similarity with those of human CYP4F2,
CYP4F3, and CYP4F8. The first 27 amino acid residues of P450 MI-3 were
highly homologous with those of monkey CYP3A8 and human CYP3A4/5/7.
Furthermore, P450 MI-2 and P450 MI-3 were recognized by anti-CYP4F and
anti-CYP3A antibodies, respectively, in immunoblot analysis and catalyzed
leukotriene B(4) omega-hydroxylation and testosterone 6beta-hydroxylation,
which are known to be mediated by CYP4F and CYP3A, respectively. Although
both enzymes had ebastine hydroxylation activity, the V(max) value of P450

MI-2 was much higher than that of P450 MI-3 (37.0 versus 0.406 nmol/min/nmol of P450), and the former K(M) (5.1 microM) was smaller than the latter K(M) (10 microM). Anti-**CYP4F** antibody **inhibited** the hydroxylation in small intestinal microsomes strongly (70%), but anti-CYP3A antibody did not. These results indicate that P450 MI-2 belongs to the CYP4F subfamily and is mainly responsible for hydroxylation of ebastine in monkey small intestinal microsomes. This suggests that the small intestinal CYP4F enzyme, P450 MI-2, can play an important role in the metabolism of drugs given orally.